Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 117-213 are pending in the application, with 117, 131, 148, 156, 164, 175, 183, 190, 197, and 207 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested. Support for these amendments can be found throughout the specification. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The Sequence Listing

In the Office Action at page 2, Examiner indicated that the present application is not in compliance with the sequence rules. Submitted herewith is a disc and paper copy of a substitute sequence listing in compliance with the sequence rules. No new matter has been added by way of the substitute sequence listing. The sequence listing on paper and in computer form are the same.

The Examiner alleges that the application discloses several reverse transcriptases from several viruses and methods of making the viruses and mutants, but no nucleic acid or amino acid sequences are disclosed. The Examiner alleges that the specification references specific amino acid residues from an amino acid sequence without identifying the amino acid sequence with a sequence identification number, for example on page 57, lines 11-12 of the specification. Applicants respectfully disagree.

According to 37 C.F.R. § 1.821(a), "[s]equences with fewer than four specifically

defined nucleotides or amino acids are specifically excluded from this section." Therefore, where Applicants have disclose amino acid sequences with four or more defined nucleotide or amino acids, Applicants have provided a sequence listing thereto and identified said sequences by a sequence identification number. Therefore, Applicants submit that the specification is in compliance with the sequence rules.

The Abstract

The Examiner has suggested that the abstract be limited to 150 words since the space provided for the abstract used by the printer is limited. Applicants have submitted a revised abstract, attached hereto, to accommodate this request.

The Title

The Examiner has alleged that the title is not descriptive (Office Action at page 3). Applicants have amended the title to "Compositions of Reverse Transcriptases and Mutants Thereof" to accommodate this request.

Objection to the Claims

The Examiner has objected to claims 148, 150-156, 158-164, 166-175, and 177-182 under 37 CFR § 1.75(d)(1) because the claims allegedly state an improper Markush group. Specifically, the Examiner alleges that various members of the Markush group in the claims are different chemical compounds and do not share a common structural feature required for the stated utility of reverse transcriptase activity (Office Action at page 3). Applicants respectfully disagree.

The Markush groups in the claims are proper as they relate to ASLV RTs and subunits thereof which have reverse transcriptase activity. *See* specification at page 3, line 27 to page 4, line 12. Therefore, this objection is in error. Withdrawal of the objection is respectfully requested.

The Examiner has objected to claims 145, 172, and 204 under 37 CFR § 1.75(d)(1) because the claims allegedly state an improper Markush group (Office Action at page 3). Applicants respectfully disagree. Claims 145, 172, and 204 properly recite components of a kit for use in reverse transcription as claimed. Therefore, this objection is in error. Withdrawal of the objection is respectfully requested.

The Examiner has also objected to claims 120-124, 126-129, 134, 136-138, 140-143, 150, 158, 166, 177, 184, 198, and 208 under 37 CFR § 1.75(d)(1) for failing to further limit the subject matter of a previous claim. Specifically, the Examiner alleges the parent claims are drawn to compositions of wild-type viral reverse transcriptases. Thus, according to the Examiner, claims 120-124, 126-129, 134, 136-138, 140-143, 150, 158, 166, 177, 184, 198, and 208 expand the scope of the claim from which they depend to include mutants and fragments (Office Action at page 3). Applicants respectfully disagree.

The Examiner has read limitations into the independent claims which are not present in the claims. Claims 117 and 131 relate to a kit or composition comprising two or more viral reverse transcriptases. Claims 148, 156, 164, and 175 relate to a recombinant ASLV RT, a kit or a composition comprising a recombinant ASLV RT that has a polymerase specific activity of at least about 30,000 units per milligram and does not contain a mutation that reduces RNase H activity. Claims 183, 197, and 207 relate to

a recombinant AMV RT, a kit or a composition comprising a recombinant AMV RT having a polymerase activity of at least about 30,000 units/mg. None of the independent claims recite the term "wild-type" as alleged by the Examiner. The dependent claims further narrow and limit the scope of the respective parent claims to relate to specific subunits and mutants and fragments of the reverse transcriptases. Therefore, the Examiner's contention is in error. Applicants respectfully request that this objection be withdrawn.

The Rejection under 35 U.S.C. § 112, First Paragraph Is Traversed

In the Office Action at page 4, the Examiner has rejected claims 120, 121, 126, 134, 140, 148, 150-156, 158, 159-175, 177-213, and 127-148 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that:

> [t]he specification, however, only provides a single representative species for the β-subunit of RSV reverse transcriptase which forms a heterodimer with the α-subunit of RSV reverse transcriptase to produce a heterodimer with substantially reduced RNase H activity. There is no disclosure of any structure of any reverse transcriptase from any source or their mutants. The specification also fails to describe additional representative species of the so called βp4 subunit by any identifying structural characteristics or properties other than forming a heterodimer with reduced RN[a]se activity relative to the wild-type.

Office Action page 4, lines 15-22. Applicants respectfully but emphatically disagree.

ASLV reverse transcriptases, which comprise AMV and RSV reverse transcriptases, comprise α and/or β subunits (specification at page 3, line 27 to page 4, line 12). The specification clearly discloses how to generate monomeric subunits, as well as the homodimeric and heterodimeric ASLV reverse transcriptases and mutants (specification page 22, lines 11-16, and especially pages 55-59, 69-76, 102, and 106). A deposit of *E. coli* DH10B(pDMAVABH-) containing a plasmid coding for the AMV RT α gene (RNase H^+) and AMV RT β gene (RNase H^-) was deposited as disclosed on page 75, lines 10-13. A deposit of *E. coli* DH10B(pDABH-His) containing a plasmid coding for a Histidine tagged RSV RT α gene (RNase H^+) and RSV RT β gene (RNase H^-) was also deposited as disclosed on page 60, lines 23-26. Using the deposited plasmids, one of ordinary skill in the art can easily produce homodimeric, heterodimeric, monomeric subunits, and mutants of ASLV RTs as claimed by Applicants using routine molecular techniques known in the art.

The βp4 subunit is an ASLV RT subunit which may be processed to produce the mature β subunit. *See* page 4, lines 23-26. At page 56, the mature β subunit construct is generated by insertion of a translational stop site in the place of the "p4" subunit cleavage site.

The sequences and function of ASLV subunits are highly conserved among the reverse transcriptases which fall into the category of the genus ASLV RT. Therefore the skilled artisan readily understands that if one method to generate a βp4 subunit of one species of an ASLV RT is taught, that same method can be used to derive other βp4 subunits from other species of ASLV RTs using routine experimentation.

The Examiner further alleges that:

> there is no disclosure of any pause site for any of the mentioned reverse transcriptases in the specification. The specification also fails to describe additional representative species of the claimed representative species by any identifying structural characteristics or properties other than having specific activity of at least 30,000 units per milligram without identifying the activity to be measured and what constitute[s] a unit of activity.

Office Action, page 4, line 34 through page 5, line 2. Applicants respectfully disagree.

Claims 121 and 135 recite the composition and kit comprising reverse transcriptases having different transcription pause sites. Contrary to the Examiner's contention, claims 121 and 135 are fully supported and exemplified at pages 34 and 66-67 of the specification. Table 1, at page 67, clearly discloses reverse transcriptases having different pause sites used in reverse transcription. Thus, one of ordinary skill in the art can readily select pairs of reverse transcriptases possessing different pause sites, as disclosed, to produce cDNAs using only routine experimentation. Therefore, claims 121 and 135 are clearly described and exemplified in the specification as claimed.

Applicants have amended claims 148, 156, 164, 175, 183, 190, 197, and 207 and their respective dependent claims to recite a "polymerase specific activity." The polymerase activity is also described at page 99, lines 10-18, of the specification. Moreover, the different levels of polymerase activities for different subunits of RTs are exemplified in Table 8 at page 106 of the specification.

Thus, the Examiner's contention that the claims are not adequately described is in error. Applicants respectfully request that this rejection be withdrawn.

The Rejections under 35 U.S.C. § 112, Second Paragraph Are Traversed

In the Office Action at page 5, the Examiner has rejected claims 117-148, 150-

156, 158-164, 166-175, and 177-213 under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that abbreviations "ASLV" and "AMV" should be defined once in the claims. Applicants have amended claim 119, to include the definitions of "ASLV," "AMV," and other abbreviations to accommodate this portion of the rejection. Therefore, withdrawal of this portion of the rejection is respectfully requested.

The Examiner further contends that the phrase "ASLV reverse transcriptase" in claims 120, 126, 134, 140, 148, 150-156, 158-164, 166-171, 175, 177-182, "specific activity . . . units per milligram" in claims 148, 151-156, 159-162, 164, 167-170, 178-181, 185-188, 190, 192-195, 197, 199-202, 207, and 209-212, and "one or more subunits" in claims 120, 126, 134, 140, 150, 158, 166, 177, 184, 191, 198, and 208 render the claims indefinite because the resulting claims do not clearly set forth the metes and bounds of the patent protection desired (Office Action at page 5, lines 13-19). Applicants respectfully disagree.

The phrase "ASLV reverse transcriptase" includes, but is not limited to, the reverse transcriptases in the specification at pages 3-4. The sequences and functions of ASLV subunits are highly conserved among the genus of ASLV reverse transcriptases (specification page 73, lines 13-16). The skilled artisan would readily understand what is meant by an "ASLV reverse transcriptase." Therefore, the metes and bounds of "ASLV reverse transcriptase" is readily understood by one of ordinary skill in the art.

With regard to the phrase "specific activity . . . units per milligram," Applicants have amended claims 148, 156, 164, 175, 183, 190, 197, and 207 and their respective

dependent claims to recite a "polymerase specific activity" further clarifying that which is being claimed. The polymerase activity is also described at page 99, lines 10-18, and Table 8 at page 106, as previously mentioned. Therefore, the claims comport with the requirements under 35 U.S.C. §112, second paragraph. Withdrawal of this portion of the rejection is respectfully requested.

The Examiner further alleges that the term "one or more subunits" is indefinite because the only enzymatically active form of the ASLV RT enzyme is a dimer and because there could not be more than two subunits per molecule of enzyme. Applicants respectfully but emphatically disagree. The specification provides evidence that each subunit of ASLV has reverse transcriptase activity, *i.e.* DNA polymerase and RNase H activities and that the catalytically active form can be an α monomer (specification at page 4, lines 10-15, and in Table 8 at page 106). Therefore, the Examiner's assertion that the only enzymatically active form of the ASLV RT enzyme is a dimer is in error. In addition, Applicants have amended the claims so they no longer recite "one or more subunits" and to further clarify that which is being claimed. Therefore, Applicants respectfully request that this portion of the rejection be withdrawn.

The Examiner has rejected claims 120, 126, 134, 140, 150, 158, 166, 177, 184, 198, and 208 as allegedly indefinite because "βp4 subunit" is not structurally defined by the specification or the claims (Office Action, page 6, lines 1-4). Applicants respectfully disagree.

As discussed above, the βp4 subunit is an ASLV RT subunit which may be processed to produce the mature β subunit. *See* page 4, lines 23-26. The mature β subunit construct may be generated by insertion of a translational stop site in the place of

the "p4" subunit cleavage site. *See* page 56. Therefore, the Examiner's contention is in error. Withdrawal of this portion of the rejection is respectfully requested.

In the Office Action at page 6, the Examiner alleges that the term "reduced" in claims 122, 127, 136, 141 and "substantially reduced" in claims 123, 128, 137, 142, are relative terms which render the claims as allegedly indefinite. Applicants respectfully disagree.

The terms "reduced" and "substantially reduced" are clearly described in the specification. *See* specification at page 33, lines 12-23. *See* also specification at page 102 (Table 7) and 106 (Table 8) where RTs with different levels of RNase H activities are exemplified. Therefore, in light of the expressed teaching of the specification, one skilled in the art clearly understands what is meant by "reduced" and "substantially reduced" RNase H activity. Reconsideration and withdrawal of this portion of the rejection are respectfully requested.

The Examiner alleges that the phrase "working concentration" in claims 144, 177, 182, 189, 196, 203, and 213 and the phrase "one or more terminating agents" in claims 145, 172, and 204 render the claims indefinite (Office Action at page 6). Applicants respectfully disagree.

The term "working concentration" is clearly disclosed in the specification at page 37, lines 3-6 and throughout the Examples, *e.g.* page 65. Moreover, it is well known to those of ordinary skill in the art of molecular biology that working concentrations of reverse transcriptases are those useful for reverse transcription reactions. Therefore, the metes and bounds of "working concentrations" are definite to one of ordinary skill in the relevant art. Reconsideration and withdrawal of this portion of the rejection are

respectfully requested.

The Examiner contends that the "only terminating agent . . . utilized by reverse transcriptase are 2',3'-dideoxy-nucleoside triphosphates . . .[t]he ordinary skill in the art would not know others and the specification does not teach any." For examination purposes, the Examiner has assumed that "terminating agents" and "dideoxynucleoside" are dideoxynucleoside triphosphates. *See* Office Action at page 6, lines 17-25. Applicants respectfully disagree.

There are other reverse transcription terminating agents known to those of ordinary skill in the art. See for example, Balzarini *et al. (Proc. Natl. Acad. Sci. USA 88:*4961-4965 (1991)) and PubMed abstracts of Neyts J. and E. De Clercq *(Biochem. Pharmacol. 47:*39-41 (1994)) and Viktorova *et al. (Mol. Biol. (Mosk) 27*:143-52 (1993)). Courtesy copies of these documents are provided herewith. Thus, the Examiner's contention that "terminating agents" can only mean dideoxynucleoside triphosphates is in error. Reconsideration and withdrawal of this portion of the rejection is respectfully requested.

The Examiner contends that claims 175 and 207 are incomplete for omitting essential steps, specifically a purification step of the reverse transcriptase from the host cell after step (b) and before step (c). *See* Office Action at page 6. Applicants respectfully disagree.

However, Applicants have amended claims 175 and 207 to further clarify that which is being claimed thereby accommodating this portion of the rejection. Therefore, reconsideration and withdrawal of this portion of the rejection are respectfully requested.

The Rejections under 35 U.S.C. § 102(b) Are Traversed

In the Office Action at page 7, the Examiner has rejected claims 148, 150-156, 158-164, 166-171, 175, 177-203, and 207-213 under 35 U.S.C. § 102(b) as being anticipated by Soltis *et al.* (*Proc. Natl. Acad. Sci. USA 85*:3372-76 (1988), IDS document AT17), and Yu *et al.* (*J. Biol. Chem. 267*:10888-10896 (1992), IDS document AR26), and Boehringer Mannheim Biochemicals Products Catalogue, pp. 92-93 (1995), IDS document AT19). In addition, the Examiner has rejected claims 148, 150-156, 158-164, 166-175, and 177-182 under 35 U.S.C. § 102(b) as being anticipated by Kotewicz *et al.* (U.S. Patent No. 5,244,797, IDS document AD1, herein as "the '797 patent"). Applicants respectfully traverse these rejections.

Independent claims 148, 156, 164, and 175 (and their respective dependent claims) relate to a recombinant ASLV reverse transcriptase, a composition, or a kit comprising a recombinant ASLV RT that has a polymerase specific activity of at least about 30,000 units per milligram and that does not contain a mutation that reduces RNase H activity. Independent claims 183, 190, 197 and 207 (and their respective dependent claims) relate to a recombinant AMV reverse transcriptase, a composition, or a kit comprising a recombinant AMV reverse transcriptase with a polymerase specific activity of at least 30,000 units per milligram.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("[t]o anticipate a claim, a reference must disclose every element of the

challenged claim and enable one skilled in the art to make the anticipating subject matter."). This burden is not met by the disclosure of either Soltis *et al.*, Yu *et al.*, Boehringer Mannheim Product Catalogue, or Kotewicz *et al.* None of the cited references discloses *a recombinant* ASLV RT that has a polymerase specific activity of at least about 30,000 units per milligram and that does not contain a mutation that reduces RNase H activity. The cited references also do not disclose a recombinant AMV reverse transcriptase with a polymerase specific activity of 30,000 units per milligram. Therefore, the claims are not anticipated by the any of the cited references. Reconsideration and withdrawal of these rejections are respectfully requested.

The Rejections under 35 U.S.C. § 103(a) Are Traversed

In the Office Action at page 8, the Examiner has rejected claims 148, 150-156, 158-164, 166-175, and 177-213 under 35 U.S.C. § 103(a) as being unpatentable over Soltis *et al.* in view of the alleged state of the art at the time the application was filed as exemplified by Chattopadhyay *et al.* (*Prot. Exp. Purification 3:*151-9 (1992), IDS document AS24). Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that "AMV-reverse transcriptase has been used extensively in biotechnology in the preparation of cDNA libraries and is a commercially viable product in the market place. Thus, one of ordinary skill in the art would have had motivation at the time of invention to produce AMV-reverse transcriptase by a recombinant method." *See* Office Action at page 8, lines 31-34. The Examiner further adds that:

> [one] ordinary skill[ed] in the art would have constructed the pRC23-p95 and pRC23-p63 taught by Soltis and coexpress

> them in a single host cell to produce the heterodimer . . . one of ordinary skill in the art would be further motivated to construct a single vector comprising the coding sequences for both the α- and β-subunits of AMV-reverse transcriptase under the control of the same promoter which would lead to the production of equal amount of the two subunits (claim 148, 150-156, 158-164, 175, 177-203, and 207-213).

Office Action page 9, lines 8-14. Applicants respectfully disagree.

Independent claims 148, 156, 164, and 175 (and their respective dependent claims) relate to a recombinant ASLV reverse transcriptase, a composition, or a kit comprising a recombinant ASLV RT that has a polymerase specific activity of at least about 30,000 units per milligram and that does not contain a mutation that reduces RNase H activity. Independent claims 183, 190, 197 and 207 (and their respective dependent claims) relate to a recombinant AMV reverse transcriptase, a composition, or a kit comprising a recombinant AMV reverse transcriptase with a polymerase specific activity of at least 30,000 units per milligram.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). In addition, the Examiner must show a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a

result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

Soltis *et al.* do not suggest or contemplate a recombinant ASLV that has a polymerase specific activity of at least about 30,000 units per milligram and that does not contain a mutation that reduces RNase H activity. Soltis *et al.* do not suggest or contemplate a recombinant AMV reverse transcriptase having a polymerase specific activity of at least 30,000 units/milligram. See Table 1 and first paragraph at page 3374, column 2. The deficiencies of Soltis *et al.* are not cured by Chattopadhyay *et al.* who also do not suggest or contemplate recombinant ASLV or AMV RTs as claimed. Chattopadhyay *et al.*, instead, disclose methods relating to HIV, thus teaching away from the claimed invention. The Examiner has not provided any factual evidence that the skilled artisan would have been motivated to derive the claimed invention with a reasonable expectation of success based on the disclosures of the cited references. Thus, the Examiner has not met the burden of establishing a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner has rejected claims 148, 150-156, 158-164, 166-175, and 177-213 under 35 U.S.C. § 103(a) as being unpatentable over the alleged fact that AMV and M-MLV reverse transcriptases are commercially available from Boehringer Mannheim Biochemicals and U.S. Biochemical in view of the state of the art at the time as exemplified by Chattopadhyay *et al.* (Office Action, pages 8-9). Applicants respectfully traverse this rejection.

The Examiner contends that:

> AMV-reverse transcriptase has been used extensively in biotechnology in the preparation of cDNA libraries and is

> a commercially viable product in the market place. The commercial preparation of AMV-reverse transcriptase may contain undesired enzymatic activities such as proteases or ribonucleases. Thus, one of ordinary skill in the art would have had the motivation at the time of invention to further purify the commercial preparation of AMV-reverse transcriptase by well known methods taught in the art such as that taught by Chattopadhyay *et al.* and preparative electrophoresis to homogeneity (claims 148, 150-156, 158-164, 175, 177-203, and 207-213). Once the ordinary skill in the art obtain[ed] the purified reverse transcriptase, he/she would have packaged it in a kit comprising buffers, primers of interest, one or more DNA polymerase to amplify the DNA product of the transcription, and one or more terminating agents for sequencing the product of transcription (claims 172-174, and 204-206).

Office Action, page 9, lines 26-37. Applicants respectfully disagree.

Independent claims 148, 156, 164, and 175 (and their respective dependent claims) relate to a recombinant ASLV reverse transcriptase, a composition, or a kit comprising a recombinant ASLV RT that has a polymerase specific activity of at least about 30,000 units per milligram and that does not contain a mutation that reduces RNase H activity. Independent claims 183, 190, 197 and 207 (and their respective dependent claims) relate to a recombinant AMV reverse transcriptase, a composition, or a kit comprising a recombinant AMV reverse transcriptase with a polymerase specific activity of at least 30,000 units per milligram.

There is no evidence in either Boehringer Mannheim Biochemicals Products Catalogue or U.S. Biochemical (cited in Yu *et al.*, *J. Biol. Chem. 267*:10888-10896 (1992), IDS document AR26) that the commercially available reverse transcriptases at the time were recombinant reverse transcriptases. This deficit is not cured by Chattopadhyay *et al.* who disclose methods relating to HIV, thus teach away from the claimed invention. There is no suggestion or contemplation of the claimed invention

based on the any of the cited references. Therefore, a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner has rejected claims 117-147 under 35 U.S.C. § 103(a) as being unpatentable over Aatsinki *et al.*[1] (BioTechniques 16:282-8 (1994), IDS document AR1) in view of the alleged facts that AMV and M-MLV reverse transcriptases were commercially available from Boehringer Mannheim Biochemicals and U.S. Biochemical, and "that HIV-1 and RSV reverse transcriptases were well known in the prior art of record, U.S. Patent No. 5,244,797 ("the '797 patent"), and in view of the state of the art at the time as exemplified by Chattopadhyay *et al.*" (Office Action, page 10). Applicants traverse this rejection.

The Examiner contends that "Aatsinki *et al.* provide one of ordinary skill in the art to use more than one reverse transcriptase in the transcription of RNA to DNA as they teach the use of . . . AMV . . . and *Thermus aquaticus* DNA-polymerase which have a reverse transcriptase activity to overcome the problems caused by pause sites." *See* Office Action, page 10, lines 11-14. Applicants respectfully and emphatically disagree.

Claims 117-147 are drawn to compositions and kits for use in reverse transcription comprising two or more viral reverse transcriptases.

Aatsinki *et al.* disclose a one step RT-PCR reaction using AMV RT and *Taq* polymerase. However, Aatsinki *et al.* do not disclose or suggest a composition or kit for

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[1]No citation was indicated for this reference. However, since Aatsinki *et al.* was cited as document AR1 in the IDS, Applicants have assumed that the Examiner is referring to the IDS document AR1 as the Aatsinki *et al.* reference being referred to here. Clarification is respectfully requested.

use in reverse transcription comprising two or more viral reverse transcriptases or uses of reverse transcriptases to overcome the problems caused by pause sites. There is no suggestion of a motivation to combine the disclosure of Aatsinki *et al.* with that of the Boehringer Mannheim Biochemicals, U.S. Biochemicals, the '797 patent, or Chattopadhyay *et al.* Moreover, the problem of pause sites was never addressed by Aatsinki *et al.* It appears that this information was gleaned from Applicants' specification using hindsight reconstruction. *See* specification page 67 where RTs with pause sites are disclosed. The Examiner is reminded that hindsight reconstruction is impermissible. The Board has stated:

> it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the Examiner's hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness. None of the cited references suggests or contemplates the invention as claimed. Therefore, the Examiner has not established a *prima facie* case of obviousness based on the cited references. Reconsideration and withdrawal of this rejection are respectfully requested.

The Obviousness-Type Double Patenting Rejections Are Traversed

The Examiner has rejected claims 148, 150-156, 158-164, 166-175, and 177-213 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of the '797 patent. The Examiner has also rejected claims 148, 150-156, 158-164, 166-175, and 177-213 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent No. 6,063,608 (herein as "the '608 patent"). Applicants respectfully traverse these rejections.

Specifically, the Examiner alleges that although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming the same subject matter or an obvious variant thereof. Applicants respectfully and emphatically disagree.

Independent claims 148, 156, 164, and 175 (and their respective dependent claims) relate to a recombinant ASLV reverse transcriptase, a composition or a kit comprising a recombinant ASLV RT that has a polymerase specific activity of at least about 30,000 units per milligram and that does not contain a mutation that reduces RNase H activity. Independent claims 183, 190, 197 and 207 (and their respective dependent claims) relate to a recombinant AMV reverse transcriptase, a composition, or a kit comprising a recombinant AMV reverse transcriptase with a polymerase specific activity of at least 30,000 units per milligram. Therefore, the claims of the present invention are clearly not obvious over the claims of either the '797 patent or the '608 patent. Reconsideration and withdrawal of these rejections are respectfully requested.

Information Disclosure Statements

In the Office Action at page 2, the Examiner indicated that many references cited in Applicants' Information Disclosure Statement filed May 20, 1999, were missing and could not be located and were not considered. Applicants will be providing courtesy copies of the missing references along with copies of the PTO Forms 1449 shortly after the filing of this reply. Applicants respectfully request that the Examiner return a copy of the initialed PTO Forms 1449 and indicate in the file that the references have been considered.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond
Attorney for Applicants
Registration No. 32,893

Date: Sept. 9, 2002

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

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SKGF Rev. 4/9/02

Version with markings to show changes made

The following claims have been amended:

119. (Once amended) The composition of claim 117, wherein said reverse transcriptases are selected from the group consisting of [MMLV, ASLV, RSV, AMV, RAV, MAV, and HIV] Moloney Murine Leukemia Virus (M-MLV), Avian Sarcoma-Leukosis Virus (ASLV), Rous Sarcoma Virus (RSV), Avian Myeloblastosis Virus (AMV), Rous Associated Virus (RAV), Myeloblastosis Associated Virus (MAV), and Human Immunodeficiency Virus (HIV) reverse transcriptases.

120. (Once amended) The composition of claim 117, wherein said reverse transcriptases comprise [one or more] an ASLV α subunit[s], [one or more] an ASLV β subunit[s], [one or more] an ASLV βp4 subunit[s], or a combination thereof.

126. (Once amended) The composition of any one of claims 122-124, wherein at least one of said reverse transcriptase comprises [one or more] an ASLV α subunit[s], [one or more] an ASLV β subunit[s], [one or more] an ASLV βp4 subunit[s], or a combination thereof.

134. (Once amended) The kit of claim 131, wherein said reverse transcriptases comprise [one or more] an ASLV α subunit[s], [one or more] an ASLV β subunit[s], [one or more] an ASLV βp4 subunit[s], or a combination thereof.

140. (Once amended) The kit of any one of claims 136-138, wherein at least

one of said reverse transcriptases comprises [one or more] an ASLV α subunit[s], [one or more] an ASLV β subunit[s], [one or more] an ASLV βp4 subunit[s], or a combination thereof.

148. (Once amended) [An] A recombinant ASLV reverse transcriptase, wherein said ASLV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram and said ASLV reverse transcriptase does not contain a mutation that reduces RNase H activity.

150. (Once amended) The ASLV reverse transcriptase of claim 148, wherein said ASLV reverse transcriptase comprises [one or more] an ASLV α subunit[s], [one or more] an ASLV β subunit[s],[one or more] an ASLV βp4 subunit[s], or a combination thereof.

151. (Once amended) The ASLV reverse transcriptase of claim 148, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 30,000 units per milligram to about 150,000 units per milligram.

152. (Once amended) The ASLV reverse transcriptase of claim 148, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

153. (Once amended) The ASLV reverse transcriptase of claim 148, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 50,000 units

per milligram to about 150,000 units per milligram.

154. (Once amended) The ASLV reverse transcriptase of claim 148, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.

156. (Once amended) A composition comprising [an] a recombinant ASLV reverse transcriptase, wherein said ASLV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram and said ASLV reverse transcriptase does not contain a mutation that reduces RNase H activity.

159. (Once amended) The composition of claim 156, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 30,000 units per milligram to about 150,000 units per milligram.

160. (Once amended) The composition of claim 156, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

161. (Once amended) The composition of claim 156, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 50,000 units per milligram to about 150,000 units per milligram.

162. (Once amended) The composition of claim 156, wherein said ASLV

reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.

164. (Once amended) A kit comprising [an] a recombinant ASLV reverse transcriptase, wherein said ASLV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram and said ASLV reverse transcriptase does not contain a mutation that reduces RNase H activity.

166. (Once amended) The kit of claim 164, wherein said ASLV reverse transcriptase comprises [one or more] an ASLV α subunit[s], [one or more] an ASLV β subunit[s], [one or more] an ASLV βp4 subunit[s], or a combination thereof.

167. (Once amended) The kit of claim 164, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 30,000 units per milligram to about 150,000 units per milligram.

168. (Once amended) The kit of claim 164, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

169. (Once amended) The kit of claim 164, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 50,000 units per milligram to about 150,000 units per milligram.

170. (Once amended) The kit of claim 164, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.

175. (Once amended) [An] A recombinant ASLV reverse transcriptase produced by a method comprising

(a) obtaining a host cell comprising one or more nucleic acid sequences encoding at least one ASLV reverse transcriptase; and

(b) culturing said host cell under conditions sufficient to produce said ASLV reverse transcriptase; and

(c) isolating or purifying said reverse transcriptase thereby obtaining said reverse transcriptase wherein said ASLV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram and said ASLV reverse transcriptase does not contain a mutation that reduces RNase H activity.

177. (Once amended) The ASLV reverse transcriptase of claim 175, wherein said ASLV reverse transcriptase comprises [one or more] an ASLV α subunit[s], [one or more] an ASLV β subunit[s], [one or more] an ASLV βp4 subunit[s], or a combination thereof.

178. (Once amended) The ASLV reverse transcriptase of claim 175, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 30,000 units per milligram to about 150,000 units per milligram.

179. (Once amended) The ASLV reverse transcriptase of claim 175, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

180. (Once amended) The ASLV reverse transcriptase of claim 175, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 50,000 units per milligram to about 150,000 units per milligram.

181. (Once amended) The ASLV reverse transcriptase of claim 175, wherein said ASLV reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.

183. (Once amended) [An AMV] A recombinant Avian Myeloblastosis Virus (AMV) reverse transcriptase, wherein said AMV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram.

184. (Once amended) The AMV reverse transcriptase of claim 183, wherein said AMV reverse transcriptase comprises [one or more] an AMV α subunit[s], [one or more] an AMV β subunit[s], [one or more] an AMV βp4 subunit[s], or a combination thereof.

185. (Once amended) The AMV reverse transcriptase of claim 183, wherein said AMV reverse transcriptase has a polymerase specific activity of about 30,000 units

per milligram to about 150,000 units per milligram.

186. (Once amended) The AMV reverse transcriptase of claim 183, wherein said AMV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

187. (Once amended) The AMV reverse transcriptase of claim 183, wherein said AMV reverse transcriptase has a polymerase specific activity of about 50,000 units per milligram to about 150,000 units per milligram.

188. (Once amended) The AMV reverse transcriptase of claim 183, wherein said AMV reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.

190. (Once amended) A composition comprising [an] a recombinant AMV reverse transcriptase, wherein said AMV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram.

191. (Once amended) The composition of claim 190, wherein said AMV reverse transcriptase comprises [one or more] an AMV α subunit[s], [one or more] an AMV β subunit[s], [one or more] an AMV βp4 subunit[s], or a combination thereof.

192. (Once amended) The composition of claim 190, wherein said AMV

reverse transcriptase has a polymerase specific activity of about 30,000 units per milligram to about 150,000 units per milligram.

193. (Once amended) The composition of claim 190, wherein said AMV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

194. (Once amended) The composition of claim 190, wherein said AMV reverse transcriptase has a polymerase specific activity of about 50,000 units per milligram to about 150,000 units per milligram.

195. (Once amended) The composition of claim 190, wherein said AMV reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.

197. (Once amended) A kit comprising [an] a recombinant AMV reverse transcriptase, wherein said AMV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram.

199. (Once amended) The kit of claim 197, wherein said AMV reverse transcriptase has a polymerase specific activity of about 30,000 units per milligram to about 150,000 units per milligram.

200. (Once amended) The kit of claim 197, wherein said AMV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

201. (Once amended) The kit of claim 197, wherein said AMV reverse transcriptase has a polymerase specific activity of about 50,000 units per milligram to about 150,000 units per milligram.

202. (Once amended) The kit of claim 197, wherein said AMV reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.

207. (Once amended) [An] A recombinant AMV reverse transcriptase produced by a method comprising

(a) obtaining a host cell comprising one or more nucleic acid sequences encoding at least one AMV reverse transcriptase; and

(b) culturing said host cell under conditions sufficient to produce said AMV reverse transcriptase; and

(c) isolating or purifying said reverse transcriptase thereby obtaining said reverse transcriptase wherein said AMV reverse transcriptase has a polymerase specific activity of at least about 30,000 units per milligram.

208. (Once amended) The AMV reverse transcriptase of claim 207, wherein said AMV reverse transcriptase comprises [one or more] an AMV α subunit[s], [one or

more] an AMV β subunit[s], [one or more] an AMV βp4 subunit[s], or a combination thereof.

209. (Once amended) The AMV reverse transcriptase of claim 207, wherein said AMV reverse transcriptase has a polymerase specific activity of about 30,000 units per milligram to about 150,000 units per milligram.

210. (Once amended) The AMV reverse transcriptase of claim 207, wherein said AMV reverse transcriptase has a polymerase specific activity of about 40,000 units per milligram to about 150,000 units per milligram.

211. (Once amended) The AMV reverse transcriptase of claim 207, wherein said AMV reverse transcriptase has a polymerase specific activity of about 50,000 units per milligram to about 150,000 units per milligram.

212. (Once amended) The AMV reverse transcriptase of claim 207, wherein said AMV reverse transcriptase has a polymerase specific activity of about 75,000 units per milligram to about 150,000 units per milligram.